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Jae/PST/thc

We refer to our appeal filed on April 20, 2001 against the decision of the Opposition Division dated February 14, 2001 in the above-referenced case. Please find enclosed 21 copies of our new Main Request and of two Auxiliary Requests. Please note that Hepworth, Lawrence, Bryer & Bizley and Mr. Bizley specifically remain the address for service in this case. It is therefore respectfully requested that the European Patent Office should continue to direct all formal correspondence and copy correspondence to Mr. Richard Bizley. Furthermore, we substantiate our appeal as follows:

INTRODUCTION

The invention claimed in the patent relates generally to the combination of recombinant DNA and monoclonal antibody technologies for the production of

non-immunogenic antibodies and their uses. The methods of the claimed invention for the first time enabled a general approach to providing improved forms of humanized antibodies that exhibit satisfactory binding capabilities while remaining substantially non-immunogenic in humans.

The prior art methods for producing humanized antibodies relied upon the presumed "self-correcting" of the framework in the assembly of the CDRs on binding of the antigen; see, for example, Verhoeyen (D37) and Verhoeyen (D35). The work of Riechmann (D36) raised questions as to what extent the framework of a given antibody can provide a passive scaffold onto which the CDRs from another antibody may be grafted and retain their antigen binding affinity. Although in Riechmann (D36) antigen binding could be improved by particular considerations on the specific antibody investigated, no conclusion could be reached on how to generally approach antibody humanization when facing substantial loss of binding affinity upon CDR grafting only. Accordingly, when summarizing the prior art, Cheetham (D40) concluded with emphasis that "[m]odifying the properties of immunoglobulin molecules may after all prove to be more a matter of 'tinkering' by molecular biology, than a tidy 'tailoring' of CDRs by the antibody engineer!"; see Cheetham (D40) on page 172, right column, last sentence. Thus, literally speaking according to Cheetham (D40), the person skilled in the art in 1988 when trying to improve CDR grafted antibodies would have no choice other than tinkering, i.e. to work unskillfully and without guidance at the improvement of CDR grafted antibodies by trial and error on a case by case basis.

In contrast, the invention claimed in the patent is based on the inventive concept that for producing humanized antibodies, the acceptor framework has to be adjusted to match the framework of the CDR donor antibody according to certain rules, in order to substantially retain the binding affinity of the donor antibody. Thus, the claimed invention provides a method for the production of humanized antibodies, wherein one or more amino acid(s) in the human acceptor framework are substituted by corresponding amino acids from the framework of the donor

antibody according to certain criteria. The claimed methods have been proven to be generally applicable and to allow the successful humanization of antibodies in numerous publications; see the documents submitted with our observations, dated April 7, 1998 and December 17, 1999. As explained in the overview at page 1 of the latter observations, the anti-Tac antibody produced in accordance with the claimed invention was the first clinically approved humanized antibody anywhere in the world. Furthermore, several humanized antibodies produced in accordance with the claimed method have now been approved for marketing, and more than 30 are currently in clinical trials. Thus, with the rules given in the claims and in the patent, the person skilled in the art no longer has to tinker by trial and error, but now has the general means and methods to tailor improved forms of humanized antibodies with therapeutic utility.

1. GENERAL REQUESTS

We request to set aside the decision of the Opposition Division dated February 14, 2001 and to maintain the above-identified patent on the basis of our new Main Request, 21 copies of which are enclosed herewith.

As a precautionary measure only, we enclose herewith two auxiliary requests. Furthermore, we reserve the right to file further auxiliary requests in case the Technical Board feels minded to object to our Main Request.

In order to expedite the proceedings, we request that an intermediate notice be issued by the Technical Board giving its preliminary opinion on the matter once it has considered the first written submissions of all parties.

As a precautionary measure, oral proceedings in accordance with Article 116 EPC are requested.

2. NEW CLAIMS REQUESTS

2.1 New Main Request

2.1.1 Claim 1

Claim 1 in the Main Request corresponds to claim 7 as granted but differs therefrom in that it contains a a final disclaiming clause at the end of the claim. The latter removes from coverage any accidental inclusion within the scope of the claim of the teachings of EP-A 0 328 404 (D48), the disclosure of which is virtually identical to that of Riechmann (D36) with respect to the matter relevant for the claim.

The wording of the disclaimer is based on the disclosure content of EP-A 0 328 404 (D48) inter alia at page 3, lines 31 to 36; Figure 2a and claims 8 and 9. Since EP-A 0 328 404 (D48) always refers to the antibody, i.e. the HuVHCAMP antibody shown in Figure 2 (hereinafter also referred to as the humanized anti-Campath-1 antibody), the disclaimer is commensurate in scope with the matter to be excluded from the subject matter of claim 1.

The reference to the published patent application is also appropriate and the most efficient way to formulate the disclaimer rather than for example to incorporate the respective amino acid sequences. Such wording of a disclaimer has been allowed in previous cases in the EPO; see for example European patent EP-B1 0 142 924 subject of T 116/95 "Insect resistant plants/MYCOGEN", dated April 26, 1999, not yet published in the OJ EPO.

2.1.2 Claims 2 to 15

Claims 2 to 15 correspond to claims 8 to 10 and 12 to 21 with back-references adjusted.

2.2 Auxiliary Request I

2.2.1 Claim 1

Claim 1 of Auxiliary Request I corresponds to granted claim 7, wherein the subject matter of granted claim 8 has been incorporated.

2.2.2 Claims 2 and 3

Claims 2 and 3 of the Auxiliary Request correspond to granted claims 9 and 10 with back-references adjusted.

2.2.3 Claim 4

Claim 4 corresponds to granted claim 12 but specifically recites the immunoglobulin heavy chain.

2.2.4 Claim 5

Claim 5 is based on the subject matter of granted claim 12 wherein the humanized immunoglobulin light chain has been defined as being obtainable by a method according to claim 3.

2.2.5 Claim 6

Claim 6 corresponds to granted claim 13 with the amendment that the reference to the light chain has been defined by being obtainable by a method of any one of new claims 1 to 3.

Since in granted claim 13 the light chain is defined by reference to granted claim 12 which in turn defined the immunoglobulin chains as being obtained by the method of any one of granted claims 7 to 10, the amendment is fully in line with the granted claims and does not extend the scope of claim 6 beyond that of corresponding granted claim 13.

2.2.6 Claims 7 to 14

Claims 7 to 14 correspond to granted claims 14 to 21 with back references adjusted.

2.3 Auxiliary Request II

2.3.1 Claim 1

Claim 1 of Auxiliary Request II corresponds to granted claim 7 but has been directed to the production of a humanized immunoglobulin light chain.

2.3.2 Claims 2 to 4

Claims 2 to 4 correspond to granted claims 8 to 10.

2.3.3 Claim 5

Claim 5 corresponds to granted claim 12 in combination with granted claim 10 and refers to the immunoglobulin light chain.

2.3.4 Claim 6

Claim 6 relates to a humanized immunoglobulin heavy chain and is based on the subject matter of granted claim 12 in combination with granted claim 10.

2.3.5 Claims 7 to 15

Claims 7 to 15 correspond to granted claims 13 to 21 with back-references adjusted.

2.4 The Claims Requests comply with the requirements of Article 123(2), 123(3) and 84 EPC

Since the claims of the Main and the Auxiliary Requests are solely based on the combination of granted claims 7 to 10 and 12 to 21, they necessarily do not extend the scope of the granted claims and are supported by the application as filed for the same reasons as the granted claims. Therefore, the claims of the main and auxiliary requests comply with the requirements of Article 123(3) and 123(2) EPC. Furthermore, since no amendments have been made to the terms in the claims, the requirements of Article 84 EPC are met as well.

3. THE NEW MAIN REQUEST DOES NOT ADD MATTER

3.1 The meaning of the term "CDRs" in granted claim 7 and in the new Main and Auxiliary Requests

In its conclusion as to Article 123(2) EPC concerning the definition of CDRs in the claims as granted, the Opposition Division on page 27, section A.7 of the written decision stated that granted claim 7 would imply the CDR definition given in granted claim 1 and therefore did not meet the requirements of Article 123(2) EPC. Furthermore, in the following section, the Opposition Division stated that reverting to the commonly accepted "Kabat" CDR definition would result in an unallowable broadening under Article 123(3) EPC.

Patentee disagrees with the Opposition Division's assessment of granted claim 7 and its dependent claims.

First of all, as acknowledged by the Opposition Division on page 24 of its written decision, section A.d6, the application as filed is in perfect agreement with Kabat's CDR definition. This is also in line with the examples of the patent which are intended to illustrate the invention. Moreover, as argued vigourously by the Opponents and accepted by the Opposition Division, the Chothia "definition" of CDR is non-standard, and not widely used by skilled persons. Thus, unless specifically defining CDR's otherwise as done in granted claim 1, the person skilled in the art when reading the application as filed and the patent specification would have inevitably understood that the CDRs in granted claim 7 referred to Kabat CDRs.

Second, as explained in section A.2 of Patentee's observations dated April 7, 1998, the invention can be expressed in a number of ways. Thus, in granted claim 1 Patentee attempted to define the contribution

of the invention as substituting one or more amino acids in the antibody variable region with corresponding amino acids from the variable region of the non-human donor antibody in addition to transferring the CDRs or hypervariable regions taking into account, as in Cheetham (D40) and Riechmann (D36), the impact of Kabat (D27) and Chothia (D28). Accordingly, in granted claim 1 the CDRs have been specifically defined as comprising the definition of hypervariable regions by both Kabat (D27) and Chothia (D28).

Alternatively, however, Patentee defined the method of the invention in terms of transferring the CDRs together with substituting from the framework region of the donor antibody amino acids that meet the important criteria as set out in features (a) to (c) in granted claim 7. In this aspect, the criteria or rules given in granted claim 7 provide the novel and inventive teaching, which has been particularly illustrated in the examples with the Kabat CDRs. The term "framework region" used twice in granted claim 7 is unambiguously defined as the portion other than the Kabat CDRs in the patent specification on page 5, lines 50 to 53 corresponding to page 10, line 37 to page 11, line 3 of the application as filed. Correspondingly, the term CDR used in this context must necessarily mean Kabat CDR. Please note that the term "framework region" was not used in granted claim 1 and therefore allowed the definition of CDRs or hypervariable regions by Kabat (D27) and Chothia (D28) in granted claim 1. However, the CDRs in granted claim 7 have never been and never were intended to refer to CDRs other than those as defined by Kabat (D27). Therefore, the term "framework region" was purposely used to indicate this.

Furthermore, granted claim 7 is an independent claim and therefore has to be assessed independently from granted claim 1. In fact, in its preliminary opinion attached to the summons of May 12, 1999 the Opposition Division in section B.3 at page 16 explicitly stated that

> "for the purpose of analyzing claim 7 ... this term [CDRs] must and will be interpreted in the commonly accepted technical sense, i.e. *Kabat's* definition of hypervariable region based on sequence variability and therefore meaning residue 31-35 for CDR1 of the heavy chain"

Accordingly, the Opposition Division in its preliminary opinion came to the conclusion that claim 7 as granted met the requirements of Article 123(2) EPC. It is quite surprising and unclear how the Opposition Division in its written decision came to just the opposite conclusion, in particular since none of the Opponents contested the Opposition Division's preliminary opinion on the term CDRs in granted claim 7 in their last written submissions. To the contrary, they heavily argued that the term CDRs in granted claim 7 could only mean Kabat CDRs and therefore that granted claim 7 lacked novelty over Riechmann (D36).

Indeed, it appears as if the Opposition Division's consideration as expressed in sections A.7 and A.8 with respect to granted claim 7 has only arisen by writing the decision, since otherwise the Opposition Division would have necessarily found the Third Auxiliary Request upon which the patent was maintained inadmissible under Article 123(2) and/or 123(3) EPC. This is because while the product directly obtained by the method of claim 1 of the 3rd Auxiliary Request, i.e. the humanized anti-Tac antibody is not affected, applying the Opposition Division's conclusion regarding the definition of CDRs in granted claim 7, the method per se would of course be affected if the meaning of the term CDRs indeed changed. This is even acknowledged by the Opposition Division in the first full paragraph on page 38 of its written decision.

Since the meaning of the term CDR has not changed in claim 1 of the Third Auxiliary Request when combining the subject matter of granted

claims 7 and 10, it can only mean that at the oral proceedings the Opposition Division must have interpreted the term CDRs in granted claim 7 as meaning Kabat CDRs since otherwise it could never have been acknowledged that the Third Auxiliary Request met the requirements of Article 123(2) EPC and 123(3) EPC. Accordingly, the statement in sections A.7 and A.8 on page 27 of the written decision must be in error.

In summary, it is Patentee's position that the term CDRs in granted claim 7 and therefore in claim 1 of the new Main Request refers and always referred to Kabat CDRs.

3.2 The disclaimer in claim 1 of the New Main Request is in line with the requirements of the EPO case law

3.2.1 The requirements for admissibility of a disclaimer in the EPO

The first Technical Board's decision dealing with a disclaimer was T 4/80, "Polyether polyols/BAYER", OJ EPO 1982, 149. In Headnote I the Board generally stated:

> "I. Originally disclosed subject-matter clearly definable by technical features, may, at the applicant's request, be excluded from a wider claim by a disclaimer, if the subject-matter remaining in the claim cannot technically be defined directly (positively) more clearly and concisely."

As explained in section 3 of the reasons, the only requirement for a disclaimer is its compliance with Article 84 EPC. This approach was and is also consistent with the practice of EPC contracting states, for example that of the UK and Germany.

In the second landmark decision T 433/86, "Modified Diisocyanat compositions/ICI", dated December 11, 1987, not published in the OJ EPO, the Board held:

> "when there is an overlap between the prior art and the claimed subject-matter defined in generic terms, a specific prior art may be excluded even in the absence of support for the excluded matter in the original documents. Such an exclusion may be achieved by way of a disclaimer, or preferably in positive terms if this leads to a clearer and more concise language" (cf. Decision T 04/80, 'Polyetherpolyols/Bayer', OJ EPO 4/1982, 149); see T 433/86 at section 2. (emphasis added)

The third leading decision T 170/87, "Hot-gas cooler/SULZER", dated 5th July 1988, OJ EPO 1989, 441, confirms this principle. It is true that Headnote II of T 170/87 states that a disclaimer cannot make an obvious teaching inventive. However, as explained by the Board in the reasons of the decision, a practical need for disclaimer exists and a disclaimer is admissible as long as the remaining subject matter is inventive. Thus, the Board explained at sections 8.4.1 to 8.4.3:

> "8.4.1 According to established Board of Appeal case law, in cases where what is claimed in general overlaps with the state of the art it is permissible to exclude a special state of the art from the claimed invention by means of a disclaimer, even if the original documents give no (specific) basis for such an exclusion (cf. Decision T 04/80, "Polyether polyols/BAYER", OJ EPO 1982, 149; also, for example, T 433/86 dated 11 December 1987, unpublished, especially point 2).
> 8.4.2 In Decision T 313/86 dated 12 January 1988 (unpublished) the Board also stated that the same principles apply when a smaller partial area of the generally defined subject-matter of the invention is to be excluded not in view of the state of the art but because it does not solve the existing technical problem (sub-section 3.5, pages 8 to 9, of the aforementioned decision).

> 8.4.3 The practice referred to in the two preceding sub-sections is justified on the basis of the following considerations: The inventive teaching originally specifically disclosed in the application is not changed as a whole merely by delimiting it with respect to the state of the art or with respect to what has proved not to be functional; rather through the disclaimer (or through a "positive" wording leading to the same result), only the part of the teaching which the applicant cannot claim owing to lack of novelty or reproducibility is "excised" in the sense of a partial disclaimer. A considerable practical need for this exists. All that is necessary is to define appropriately what under the given circumstances is left of the inventive teaching originally disclosed that is still capable of being protected." (emphasis added)

Hence, this decision, which is often relied upon by the Technical Boards of Appeal in recent decisions, provides no basis for the requirement that the prior art to be removed from coverage must be "accidental" and no longer relevant for the assessment of inventive step. To the contrary, the concept and even need of disclaimers for protecting an inventive teaching is confirmed.

Regarding the requirements of Article 123(2) EPC, the Enlarged Board of Appeal G 1/93, "Limiting feature/ADVANCED SEMICONDUCTOR", OJ EPO 1994, 541 held in section 16 of the reasons that the addition of an undisclosed feature limiting the scope of protection conferred by a patent, i.e. a disclaimer, does not violate Article 123(2) EPC if the feature in question merely excludes protection for part of the subject-matter of the claimed invention as covered by the application as filed and does not provide a technical contribution to the claimed subject-matter.

Accordingly, the requirements for the admissibility of the introduction of a disclaimer in light of the leading decisions T 4/80, T 433/86 and T 170/87 and G 1/93 are that:

(1) the claimed subject-matter cannot technically be defined positively more clearly and concisely;
(2) the disclaimer limits the scope of protection of the original and granted claims; and
(3) the feature of the disclaimer does not provide a technical contribution to the claimed subject-matter.

Accordingly, the Guidelines for Examination in the European Patent Office clearly state that an element clearly defined by technical features may be expressly excluded from the protection claimed, for example, in order to meet the requirement of novelty; see the Guidelines part C, Chapter III, section 4.12.

As we will show in the following, the above conditions are met by our new Main Request.

3.2.2 Patentee is entitled to disclaim the subject matter relevant under Article 54(3)(4) EPC of the earlier patent application EP-A 0 328 404 (D48)

EP-A 0 328 404 (D48) was filed on February 10, 1989, claiming the priority of two earlier British applications of February 12 and 25, 1988. Since the application was published only after the relevant second priority date of the present patent but has an earlier filing date, it constitutes prior art under Article 54(3) (4) EPC. It therefore is relevant for the assessment of novelty only and not for inventive step.

EP-A 0 328 404 (D48) teaches the preparation of the humanized anti-Campath-1 antibody, wherein in the heavy chain of the acceptor framework substitutions are to be made at positions 27 or 30 or both; see also section 2.1.1, supra. These two amino acid substitutions incidentally happen to meet the criteria of the method of granted claim 7, i.e. claim 1 of the new Main Request. Since it is not possible to positively distinguish the new and inventive method of claim 1 of the

new Main Request from the incidental disclosure in EP-A 0 328 404 (D48), the relevant subject matter from this application has been excluded from the protection by means of a disclaimer in accordance with the rationale as set forth, for example, in T 433/86.

First, as already discussed in section 2.1.1, supra, the subject matter of the disclaimer is supported by and exactly corresponds to the relevant disclosure in EP-A 0 328 404 (D48). Furthermore, the disclaimer has been formulated in a clear and concise manner.

Second, the disclaimer clearly limits the scope of protection of the original and granted claims.

Third, in view of the fact that the disclaimer merely removes from coverage a particular embodiment incidentally happening to fall within the scope of granted claim 7, the subject matter of the disclaimer is not a feature that provides a technical contribution to the claimed subject matter.

Fourth, since EP-A 0 328 404 (D48) is citable only for novelty, once the claimed subject matter has been delimited from the relevant disclosure of this document it is no longer relevant.

Fifth, although a scientific publication Riechmann (D36) corresponding to EP-A 0 328 404 (D48) exists, it is entirely appropriate to formulate a disclaimer on the basis of EP-A 0 328 404 (D48) rather than on the basis of Riechmann (D36). This is because Riechmann (D36) describes only two embodiments which incidentally fall within the scope of claim 1, i.e. a heavy chain with a substitution at position 27 and a heavy chain with substitutions at positions 27 and 30. In contrast, due to, for example, the wording of claims 8 and 9, EP-A 0 328 404 (D48) discloses in addition a heavy chain with the substitution at position 30

only. Therefore, the relevant disclosure in EP-A 0 328 404 (D48) is broader than that of Riechmann (D36). It is therefore all the more justified to base the disclaimer on the disclosure of EP-A 0 328 4O4 (D48).

Furthermore, it has been the continuous practice of the EPO to generally allow disclaimers for subject matter disclosed by an earlier application under Article 54(3)(4) EPC; see for example Singer/Stauder, EPÜ Artikel 84, section 19-21 "4. Disclaimer". If thereby the disclosure content of Riechmann (D36) is inevitably excluded as well, this does not harm the allowability of the disclaimer for the disclosure of EP-A 0 328 404 (D48). However, even if account is taken of the fact that Riechmann (D36) is prior art under Article 54(1)(2) EPC, this does not change the conclusion that the disclaimer in the new Main Request meets the requirements of the EPC.

3.2.3 The disclaimer in claim 1 is commensurate with the teaching of EP-A 0 328 404 (D48) and of Riechmann (D36)

As mentioned in section 3.2.2, supra, EP-A 0 328 404 (D48) and the corresponding scientific publication Riechmann (D36) disclose the preparation of the humanized anti-Campath-1 antibody, wherein in the heavy chain of the acceptor framework substitutions have been made at positions 27 and/or 30; see also the discussion of Riechmann (D36) and EP-A 0 328 404 (D48) in sections F.1.1 and F.1.4 respectively of Patentee's observations dated April 7, 1998, and the Opposition Division's characterization of Riechmann (D36) in its written decision. These two amino acid substitutions incidentally happen to meet the criteria of the method of claim 7 as granted, i.e. claim 1 of the new Main Request.

Nowhere in EP-A 0 328 404 (D48) and Riechmann (D36) is there disclosed or suggested the substitution of an amino acid residue in the Kabat-framework other than residues 27 and 30 for the particular HuVHCAMP antibody. This has also been acknowledged by the Opposition Division on page 34 of its written decision where it is stated:

> "**D36** discloses the preparation of a specific humanized antibody and there is no explicit universal teaching which the authors conclude could be applicable to the preparation of other humanized antibodies. What the skilled person would learn from **D36** is simply that, in order to increase binding affinity, amino acid residues 27 and 30 of a particular human acceptor framework have been substituted for their rat counterparts. ...
>
> In the last sentence of page 236/left column/middle paragraph of **D36**, the authors observe that '... *alterations in the 'Kabat' framework regions can enhance the affinity of the antibody ...*' (underlining added), thereby indicating that their conclusion only applies to the anti-CAMPATH-1 antibody they have prepared. Even the section "Prospects" on page 327 of **D36** only relates to potential therapeutic implications of the same particular humanized anti-CAMPATH1 antibody;" (emphasis added in the first paragraph)

In fact, the disclaimer has now been worded as requested by the Opposition Division on page 35 of its written decision. That is to "recite what **D36** teaches, namely 2 amino acid substitutions at positions 27 and 30 in the heavy chain of a humanized anti-CAMPATH1 antibody"; see the penultimate paragraph on page 35.

3.2.4 EP-A 0 328 404 (D48) and Riechmann (D36) do not provide a solution to the problem

There is not any indication in EP-A 0 328 404 (D48) and Riechmann (D36) which could suggest a solution to the envisaged technical problem, viz. that the affinity of a given humanized antibody for therapy could be substantially improved by employing substitutions of amino

acid residues in the Kabat framework according to the rules of claim 1. Indeed, according to the Opposition Division, involvement of an inventive step would have to be recognized. Hence, on page 44 and 45 of its written decision the Opposition Division stated:

> "**D36** discloses the preparation of a **particular** humanized antibody and there is no explicit universal teaching which the authors conclude could be applicable to the preparation of other humanized antibodies. What the skilled person would learn from **D36** is simply that, in order to increase binding affinity, amino acid residues 27 and 30 of a particular human acceptor framework have been substituted for their rat counterparts. The authors of **D36** were not aware of the fact that their substitution strategy could be formulated in a more generic manner to yield substitution 3 criteria (a) – (c) according to claim 1 of the third auxiliary request. Hence, they neither proposed that a similar strategy could be used when attempting to humanize other antibodies, nor that further amino acid substitutions deep in the *Kabat* framework should be made.
>
> While it is true that the publications of Chothia (**D28**), Roberts (**D31**), Amit (**D23**), Verhoeyen (**D37**), Cheetham (**D40**) and Winter (**D32**), in the wider context of engineering the antigen binding site and maintaining or improving antibody affinity, identify potential problems with some particular amino acids in the *Kabat* framework, none of them provides a universal solution by formulating substitution rules similar to the 3 criteria (a) – (c) of claim 1 and suggesting that such rules could be employed in antibody humanisation"; see the paragraph bridging pages 44 and 45 and the following paragraph. (emphasis in bold by the Opposition Division)

For the time being, let it be observed that the teaching of Riechmann (D36) and the corresponding application EP-A 0 328 404 (D48) does not contain any suggestions going beyond what has been actually disclosed and disclaimed from the scope of claim 1. This is also evident from the review article "Engineering of antibodies" (D35) authored by Dr. Riechmann together with another renowned scientist, Dr. Martine

Verhoeyen, author of Verhoeyen (D37). Though these two leading scientists in the field had access to all relevant art at the priority date of the Patent and had even more information at hand than was available to the general public, they did not suggest, let alone disclose, the possibility of humanizing antibodies by altering framework amino acids according to the rules of the Patent. In this respect, we would like to note that in contrast to usual publications, review articles like that of Drs. Verhoeyen and Riechmann (D35) are not subject to a reviewing process by referees but are an opportunity to present speculation and outlook for future embodiments. Drs. Riechmann and Verhoyen made it very clear what for them was possible in the field of antibody engineering. Figure 3 of (D35) represents their imagination of possible novel versions of antibodies. At the top of this figure it is even emphasized to the person skilled in the art what at that time was thought to be possible: "only CDRs are murine"! It can hardly be true that the average person skilled in the art should be able to conceive more than what was thought and disclosed to be possible by two leading scientists in this field.

3.3 The recent case law is not applicable to the present case

Regarding the case law of the Boards of Appeal on the allowability of disclaimers, the Opposition Division in section B.3.c1 on page 32 of the written decision referred to two recent decisions of the Technical Board 3.3.2, T 863/96 and T 596/96. In view of the reasoning in these two decisions, the Opposition Division came to the conclusion that the case law of the Boards of Appeal may not permit a disclaimer in the present case because Riechmann (D36), the disclosure of which is inevitably removed by the disclaimer of (D48), would still be the "piece of prior art coming closest to the claimed subject matter"; see last paragraph on page 32 of the written decision. However, we respectfully submit that this statement is contrary to the facts and the Opposition Division's own assessment of the teaching of Riechmann (D36).

3.3.1 The Opposition Division's interpretation of the case law regarding the admissibility of disclaimers was not correct

The decisions T 863/96 and T 596/96 as interpreted and applied by the Opposition Division would be in conflict with the interpretation of the EPC by other Appeal Boards and therefore give rise to important general questions on the uniform application of the law and corresponding national law of the EPC contracting states. In this context we would be happy to provide a summary of the EPO case law, which will show that disclaimers have always been permitted when their objective was to distinguish over the prior art disclosure and where no positive features are available to define the remaining subject matter more clearly and concisely; see also section 3.2.1, supra. Thus, if the disclaimer was clear under Article 84 EPC, had a basis in the prior art to be removed, and the scope of the claims was restricted without changing the nature of the originally claimed invention, it has been the continuous practice of the Technical Boards of Appeal to allow the introduction of a disclaimer. As mentioned before, this is also consistent with jurisprudence in the contracting states of the EPC.

In any case, both cases referred to by the Opposition Division have their own merits and are not applicable to the present situation.

In T 0863/96-3.3.2, "Deprenyl/SOMERSET PHARMACEUTICALS", dated February 4, 1999, not yet published in the OJ EPO, the Board actually did not need to take a decision on the allowability of a disclaimer. It merely expressed its doubts because the prior art document dealt with the same drug of the there claimed invention and its use for the same therapeutic indication; see section 3.2 of T 0863/96.

In the fact situation underlying T 0596/96-3.3.2, "Pro-liposome/PHARES PHARMACEUTICAL", dated December 14, 1999, not yet published in the OJ EPO, a first condition for the allowability of the introduction of a disclaimer, i.e. that the prior art document is indeed novelty-destroying, had not been met.

Thus, the fact situations underlying the mentioned decisions considerably differ from the present case.

Regarding the general applicability of the catchword of T 863/96 quoted by the Opposition Division in section B.3.c1, i.e. that the disclaimed prior art document "must then disappear from the prior art field to be taken into consideration", we emphatically disagree. It might be that in the fact situation underlying T 863/96 the Appeal Board 3.3.2 had reasons to take such a view on the allowability of disclaimers, but there is no history of case law by the Technical Boards (!) which would permit this restrictive interpretation in general. To the contrary, the Appeal Board 3.3.3 held in decision T 434/92- 3.3.3, "Molded articles/AMOCO CORPORATION", November 28, 1995, not published in the OJ EPO, in section 5.2 of the reasons:

> "The function of a disclaimer is to excise a portion of the subject-matter of an already existing claim, for instance to exclude an area of prior disclosure. In this connection, the Board is not aware of anything in the cited decision T 0004/80 or elsewhere, which would justify a general requirement for there to be "no real relationship" of the disclaimer to the novelty destroying subject-matter (cf. decision under appeal, Reasons for the decision, para. 2.2.3.1).
>
> Whilst the decision under appeal does not define precisely what is meant by "no real relationship", nevertheless if there were no relationship at all between the subject-matter of a claim and that of a disclaimer, the latter would clearly not succeed in its function of excising part of the former. Consequently, the fact alone that the subject-matter excised by a

disclaimer is related in some way to that remaining after excision is not a justified objection to the introduction of a disclaimer." (emphasis added)

3.3.2 Riechmann (D36) does not come closest to the claimed invention

In this respect, we would like to note that as discussed above and acknowledged by the Opposition Division in its written decision, Riechmann (D36) does not disclose a general method for humanizing an antibody. Consequently, this document cannot necessarily be a document which comes closest to the claimed invention. It merely comes close to a result obtainable by the claimed method but not at all to the claimed method itself. This seems a subtle but is an important difference!

Accordingly, documents which generally address the problem of humanizing antibodies would have to be considered as the closest prior art. Notably, as summarized in section F.1. of the written decision, the Opponents when discussing inventive step of the anti-Tac antibody of the invention did not cite Riechmann (D36) as the document the person skilled in the art would have considered when trying to humanize a given antibody; see also the minutes at section 15. Thus, not even the Opponents were able to derive a teaching from Riechmann (D36) that could be applied to any other antibody.

For the above reasons, it is submitted that the claims of the new Main Request meet the requirements of the EPC.

4. AUXILIARY REQUEST I

As explained in section 2.2, supra, claim 1 of the First Auxiliary Request combines the subject matter of granted claims 7 and 8, thereby requiring that at least three substitutions are to be made in accordance with any one of rules (a) to (c). This feature positively distinguishes the subject matter of claim 1 from EP-A 0 328 404 (D48) and Riechmann (D36) which disclose one and two amino acid substitutions in the heavy chain of the humanized anti-Campath-1 antibody; see also section 3.2.3, supra.

As regards the meaning of the term "CDRs" in claim 1 of Auxiliary Request I we refer to section 3.1, supra.

In summary, claim 1 and dependent claims 2 to 14 of the first Auxiliary Request meet the requirements of the EPC.

5. AUXILIARY REQUEST II

As mentioned in section 2.3, supra, claim 1 of Auxiliary Request II corresponds to granted claim 7 but has been directed to the production of a humanized immunoglobulin light chain. Since EP-A 0 328 404 (D48) and Riechmann (D36) disclose amino acid substitutions only in the heavy chain of the humanized anti-Campath-1 antibody, the subject matter of claim 1 is novel over the teaching of those documents.

Furthermore, this restriction implies that the issue of whether or not reference to CDRs in this claims request could possibly represent an inadmissible broadening under Article 123(2) and/or 123(3) EPC is moot. That is because each of the three respective light chain Chothia "CDRs" or "hypervariable regions" (Chothia (D28)) is contained *within*

the respective Kabat CDR, so that "CDR's as defined by Kabat together with Chothia" means exactly the same as Kabat CDRs.

Therefore, the claims of Auxiliary Request II meet the requirements of the EPC.

6. ASPECTS OF PATENTABILITY

Aspects of patentability, i.e. enabling disclosure, novelty and inventive step are, of course, clearly in accordance with the submissions made by Patentee with its observations on April 7, 1998 and December 17, 1999. Further comments are unnecessary at this point.

7. SUMMARY

To summarize, in the opposition proceedings the Patentee has not been allowed to defend the patent on the basis of a claims request commensurate with the contribution of the invention as taught in the patent. With the amendments to the claims and the explanations given above, it is submitted that the patent meets the requirements of the EPC. Our request to set aside the decision of the Opposition Division and to maintain the patent on the basis of the new main request is therefore fully justified.

Dr. Hans-Rainer Jaenichen
European Patent Attorney

Encl.:
21 copies of the new Main Request
21 copies of Auxilary Requests I and II
18 copies of the Appeal Brief